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Noninvasive ventilation in pulmonary rehabilitation of COPD patients☆

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Summary
Noninvasive positive pressure ventilation (NIPPV) has been shown to improve exercise tolerance and health-related quality of life in patients with advanced COPD. This study tested the feasibility of nocturnal NIPPV as an additional tool in a hospital-based pulmonary rehabilitation program. This prospective observational trial included forty COPD patients in GOLD stage IV. NIPPV was successfully introduced and accepted during sleep by all patients. All patients received pressure support ventilation for 7.9 ± 0.5 h per day with an inspiratory support of 17.5 ± 4.4 cmH_2O, and an expiratory pressure of 4.5 ± 0.9 cmH_2O. The outcome of pulmonary rehabilitation in patients receiving nocturnal NIPPV was compared with the results of forty matched control patients who underwent the same program. Rehabilitation with nocturnal NIPPV resulted in the 6-minute walk test and in the longest non-stop walk distance in improvements of 82 and 89 m, respectively, while patients without nocturnal ventilatory support improved by 50 and 51 m ($p < 0.04$ and $p < 0.03$ between groups, respectively). Further significant improvements were found for FEV_1, lung hyperinflation, and blood gases in the NIPPV treated, but not in the control subjects. Health-related quality of life, assessed by the SF-36 questionnaire, improved moderately or largely in patients receiving NIPPV in the categories role-physical, vitality, social function, and mental health. Control subjects improved moderately in vitality only. In conclusion, nocturnal NIPPV is feasible and enhances the effects of pulmonary rehabilitation in advanced stage COPD.

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Introduction

Exercise intolerance is one of the most disabling factors in patients with advanced chronic obstructive pulmonary disease (COPD). Dyspnoea and/or fatigue are the most important symptoms, resulting from impaired pulmonary gas exchange, ventilatory insufficiency, peripheral muscle dysfunction, cardiac dysfunction, or any combination of the above. Anxiety and poor motivation may further attenuate exercise tolerance.[1]

Pulmonary rehabilitation (PR) is an important part of the management of advanced COPD.[2] Randomized controlled trials have shown that 3—12 weeks PR can reduce respiratory symptoms, improve exercise tolerance, improve quality of life, and suggest that PR reduces the number of hospitalizations.[3—5]

Noninvasive positive pressure ventilation (NIPPV) has been suggested as an additional technique to enhance functional capacity[6] and sleep quality[7] in advanced COPD patients. Significant improvements in 6-minute walk distance (6MWD) could be achieved in previous rehabilitation programs when exercise training was performed during the application of NIPPV.[8,9] However, performing mask ventilation during exercise training is associated with practical difficulties. Only selected patients are able to comply with the requirements of exercising *and* noninvasive ventilation. To circumvent these practical disadvantages, and to take advantage of the potential impact of NIPPV on sleep quality, NIPPV and training were timely separated. Similar to two previous clinical trials,[10,11] NIPPV was provided during sleep.

The aim of this study was to evaluate the feasibility of nocturnal NIPPV as an additional treatment option in patients with severe COPD during hospital-based PR. In addition, the impact of NIPPV on functional status, lung function, and health-related quality of life (HRQL) was assessed.

Patients and methods

Patients, setting, and design of the study

This trial was designed as a prospective observational study. Successive COPD patients in GOLD stage IV,[1] receiving optimized medical treatment and long-term oxygen treatment[12] were recruited at a large, specialized rehabilitation hospital (Klinikum Berchtesgadener Land, Schoenau, Germany) from January to December 2006. Subjects were not considered for this study if they had previous NIPPV treatment or CPAP for obstructive sleep apnoea, severe orthopaedic or neurologic problems that reduce mobility or cooperation with physical training, poor controlled coexisting psychiatric or unstable cardiac disease, and acute exacerbation of COPD at any time during PR. Acute exacerbation was defined according to Madison[13] and Anthonisen[14] characterized by increased breathlessness in combination with worsening of cough and sputum production, change in the colour of the sputum, and rising levels of C-reactive Protein (CrP). All patients gave informed consent prior to inclusion into the study.

The outcomes of functional assessments and HRQL were compared with the results of a control group consisting of the same number of matched COPD patients not receiving NIPPV. Control subjects were recruited from a pool of 230 stable, nonexacerbated COPD patients who also received optimized medical treatment and oxygen, and who completed the same PR program (see below) since January 2005. Patients who would not have received NIPPV due to one or more of the above-described exclusion criteria were not included into the pool of possible control patients. Matching criteria were sex, age (±5%), body mass index (BMI; ±10%), baseline 6-minute walk distance (±5%), and baseline PCO_2 (±5%).

The study protocol in its final version was approved by the institutional ethics committee. It is registered at ClinicalTrials.gov (ID NCT00710463).

Interventions

Rehabilitation program: hospital-based PR was performed according to a fixed protocol, which was uniformly applied to all subjects (NIPPV group and controls) at five days of the week. The program consisted of supervised sessions of aerobic upper and lower extremity endurance training. Lower extremity exercising was performed on a treadmill or on a cycle ergometer. The sessions were performed over up to 60 min, including warm-up and cool-down exercises. In addition, patients received 30—45 min training intervals, including individually tailored strength training, diaphragmatic breathing and controlled coughing exercises, along with activating physiotherapy. Twice per week, all patients participated in education programs about self-management and nutrition, and underwent reviews of the proper use of NIPPV, oxygen therapy and inhalers.

Noninvasive ventilation: NIPPV was performed with a BiPAP Synchrony® (Respironics Inc., Murrysville, PA, United States) or a VPAP III ST-A® (Resmed Ltd, Bella Vista NSW, Australia) ventilator in pressure support ventilation mode. The aim of ventilation was a reduction of resting PCO_2 during spontaneous breathing by at least 10%, or into the normal range (35—45 mmHg). Measurements for determination of the resting PCO_2 were performed at admission, and follow-up measurements were performed in the morning after nocturnal NIPPV, 2 h after switching from mask ventilation to spontaneous breathing.

In the first days of treatment, inspiratory and expiratory pressures were carefully up-titrated to obtain the best ventilatory support. However, a minimum inspiratory pressure of 16 cmH_2O and a minimum expiratory pressure of 4 cmH_2O must have been reached at the third day of treatment.[15] Patients without hypercapnia were ventilated with these minimum pressures. Patients were advised to use the ventilator for at least 6 h every day, preferably during sleep at night. Best fitting nasal or full face masks (Ultra Mirage II™ series, Resmed, Bella Vista NSW, Australia) were selected according to the patient's tolerance. Oxygen was inserted into the ventilatory circuit in a flow rate that kept the oxygen saturation during NIPPV at or above 90%. In case of difficulties in the adaptation process of NIPPV, patients were studied with polysomnography (including capnography) to optimize NIPPV during sleep.

Assessments

Feasibility of NIPPV was determined by daily assessment of patients' adherence to NIPPV, and by measurement of the average daily usage of NIPPV. The usage was calculated by reading the hour meter of the ventilator at baseline and at the end of the study.

Lung function and blood gases: spirometry and body plethysmography (MasterScreen Body, Jaeger GmbH, Hoechberg, Germany) were performed following the guidelines of the American Thoracic Society[16,17] using reference values of the European Respiratory Society.[18] Blood gases were analyzed (Radiometer ABL800, Willich, Germany) at rest from the hyperaemic earlobe.

Functional capacity: six-minute walk distance was determined based on the guidelines of the American Thoracic Society.[19] After a phase of recovery, patients were instructed to walk at their fastest pace and to cover the longest possible distance over 6 min. Oxygen saturation was continuously monitored, and supplemental oxygen was supplied to keep oxygen saturation $> 90\%$. The oxygen cylinder or liquid oxygen container was carried by a separate person. The test was performed on a 30-m corridor by technicians with specific experience. Patients who became symptomatic (e.g., severe dyspnoea or physically exhaustion) were instructed to stop and to continue as soon as possible. For the 6MWD, the minimal clinically important difference before and after PR was not yet firmly established. Depending on the source, it had been considered to be 35 m[20] or 54 m.[21] The distance walked until the first stop was defined as the longest non-stop walk distance.

Health-related quality of life (HRQL) was assessed with the self-administrated generic questionnaire SF-36,[22–24] which consists of 36 questions covering eight health concepts: physical function, bodily pain, role-function physical, general health perceptions, vitality, social function, role-function emotional, and mental health. In addition, there are two summary scores, one for physical activity, and one for mental health. For all measures of the health components, scores were transformed linearly to scales of 0–100, with 0 indicating maximal impairment and 100 indicating the minimal impairment.

Statistical analysis

Values are presented as mean $\pm$ SD. For all tools, the values obtained at baseline and after PR were compared using a paired *t*-test, unpaired *t*-test, the Wilcoxon matched pairs test, or the Mann–Whitney test, as appropriate. Correlations were calculated by using Pearson's correlation test. For all tests, $p < 0.05$ was considered significant. The statistics were completed using a standard statistical package (SPSS-software Version 13.0, SPSS Inc., Chicago, IL, USA).

Clinically meaningful changes for the largest non-stop walk distance and the SF-36 scores have not been defined in pulmonary patients. One independent method of assessing the magnitude of change is the effect size (ES), which is a standardized measure of change within a group. The effect size is calculated by dividing the mean change from the initial score to the follow-up score by the SD of the initial score, as follows: (Mean Initial Score − Mean Follow-up Score)/SD of Initial Score.[25] While the magnitude of the effect size that is clinically relevant for specific health parameters has yet to be established, Cohen[26] and others [27,28] have suggested that an effect size of 0.20 is small, 0.50 is moderate, and >0.80 is large. Thus, the greater the effect size, the stronger is the evidence that a change represents a minimal clinically meaningful difference.

Results

During the one-year study period, 55 consecutive patients in GOLD stage IV were screened. Forty-three patients met all in- and exclusion criteria and were enrolled into this study. Three subjects developed an acute exacerbation of COPD and terminated the study prematurely. These patients were not included into the final data analysis. Forty patients fulfilled all requirements.

NIPPV could be successfully introduced and continued over the whole period of PR in all 40 patients. Within three days after initiation of NIPPV, all patients felt comfortable with the selected mask and the ventilatory mode (pressure support ventilation). The average inspiratory pressure was 17.5 ± 4.4 cmH_2O, and expiratory pressure was 4.5 ± 0.9 cmH_2O. The average use of NIPPV was 7.9 ± 0.5 h per day. All subjects exceeded the minimum ventilatory pressure limit of 16/4 cmH_2O and the minimum daily ventilator usage time of 6 h. Sixteen subjects, in whom the requested CO_2 reduction was not reached by day 3, were observed with polysomnography over one or two nights. Nocturnal optimisation of NIPPV resulted in all subjects in the CO_2 target required by the protocol.

The functional capacities and the HRQL of the 40 prospectively studied patients were compared to 40 control subjects, who were matched according to the criteria described above. At baseline, no statistically significant differences could be found for patients in either group for gender distribution, age, BMI, 6MWD, blood gases, lung function, and the largest non-stop walk distance (Table 1).

Pulmonary rehabilitation was performed over 29.5 ± 6.5 and 29.3 ± 5.9 days in patients undergoing PR plus nocturnal NIPPV *versus* PR alone, respectively ($p = 0.54$).

The 6MWD increased on average by 50 m in the control group, compared to 82 m in the NIPPV group ($p < 0.04$, Fig. 1). The largest non-stop walk distance increased by 51 m in the control group, while the NIPPV group increased by 89 m ($p < 0.03$, Fig. 2). The effect size determination of the improvements in both tests indicates large and moderate improvements in PR patients with NIPPV, compared to moderate and small improvements for PR patients without NIPPV (Table 2). The minimal clinically important difference in the 6MWD of 35 m[20] was reached by 78% of the subjects in the NIPPV group, versus 58% in control group subjects.

During PR, patients with NIPPV demonstrated significant improvements in blood gases and in the measurement of the quotient of Residual Volume and Total Lung Capacity (RV/TLC), a surrogate of lung hyperinflation, while FEV_1 and FEV_1% predicted improved without reaching statistical significance. In contrast, spirometry, body plethysmography, and blood gases did not change relevantly within control subjects (Table 2). The improvements of functional capacity

Table 1 Subject characteristics at baseline.

		PR with NIPPV, $n = 40$	PR without NIPPV, $n = 40$	p-Value
Sex (m/f)	Male/female	18/22	20/20	n.d.
Age	[years]	57.9 ± 9.1	56.8 ± 8.0	0.53
BMI	[kg/m^2]	21.7 ± 4.6	22.3 ± 3.8	0.7
LTOT flow rate	[l/min]	3.7 ± 0.8	3.4 ± 0.9	0.56
Post-bronchodilator FEV_1	[l]	0.72 ± 0.26	0.69 ± 0.18	0.81
Post-bronchodilator FEV_1	% of predicted	26.4 ± 11.4	25.5 ± 7.2	0.54
TLC	% of predicted	131.4 ± 25.6	139.2 ± 12.5	0.41
RV/TLC	%	75.2 ± 8.7	76.7 ± 6.5	0.75
pO_2[a]	[mmHg]	53.4 ± 7.6	56.2 ± 7.4	0.19
PCO_2[b]	[mmHg]	53.2 ± 9.8	51.7 ± 7.8	0.22
Patients with $PCO_2 \leq 45$ mmHg	*n*	7	9	
Patients with $PCO_2 > 45$ mmHg and ≤ 50 mmHg	*n*	7	5	
Patients with $PCO_2 > 50$ mmHg	*n*	26	26	
6MWD	[m]	243 ± 91	245 ± 88	0.97
Largest non-stop walk distance	[m]	219 ± 116	210 ± 115	0.81

PR: pulmonary rehabilitation, NIPPV: noninvasive positive pressure ventilation, BMI: body mass index, LTOT: long-term oxygen treatment, FEV_1: forced expiratory volume in the first second, TLC: total lung capacity, RV: residual volume, 6MWD: 6-minute walk distance, and n.d.: not done.

[a] Measured during rest while breathing room air.

[b] Measured during rest with the prescribed flow rate of oxygen.

did not correlate with changes in blood gases, chest-hyperinflation (RV/TLC), or with FEV_1 (data not shown).

Noninvasive ventilation was applied independently of baseline PCO_2. Subgroup analysis of all patients with $PCO_2 \leq 50$ mmHg revealed that NIPPV produced similar treatment effects in patients above or below this threshold (Table 3).

Quality of life measurements were performed with the SF-36 questionnaire in 35 patients in the NIPPV group and in 34 control group subjects. Patients with NIPPV treatment had worse baseline scores for bodily pain, vitality, social function, role-function emotional, mental health, and the mental component summary score, compared to the control group. Patients with NIPPV revealed clinically relevant improvements (moderate or large effect sizes) in 4 categories of the SF-36 questionnaire and in one summary score, while control subjects reported a relevant improvement in the category 'vitality' only (Fig. 3 and Table 4).

Discussion

The addition of nocturnal NIPPV treatment to a hospital-based, intensive PR program is feasible and accepted by patients with advanced COPD. Our study supports the previously documented, beneficial effects of PR on functional capacity and HRQL.[3] In addition, the present findings suggest that the effects of an intensive, three to five weeks, inpatient rehabilitation program can be extended, if patients receive nocturnal NIPPV, although the results of our secondary outcome parameter 6MWD, longest non-stop walk distance, and HRQL had been compared to a historical control group.

The professional environment of a rehabilitation hospital might have been an important reason for the successful NIPPV implementation and adherence of patients to this treatment. Careful uptitration of pressure support might have been the reason for the achievement of satisfactory ''doses'' of NIPPV, judged from average use of NIPPV of 7.9 h per day and the pressure levels applied. With the special setting, design and the close observation of patients, this study avoided the shortcomings of a previous study with similar treatment intention,[29] which failed to

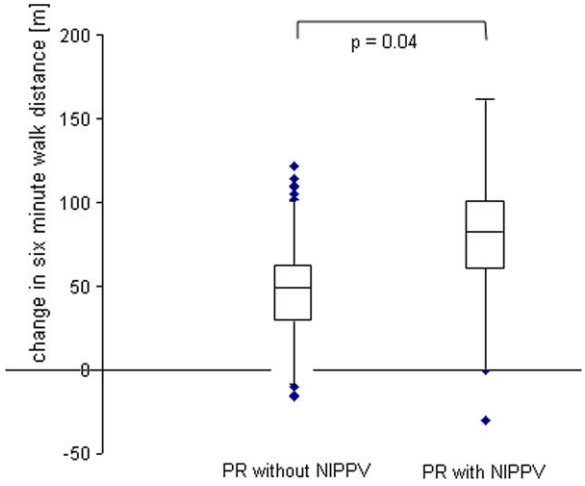

Figure 1 Changes in the six-minute walk distance from baseline to the end of a 29-day, hospital-based, intensive pulmonary rehabilitation (PR) program. Patients who had been started on nocturnal NIPPV at the beginning of the rehabilitation program (right) revealed significantly better increases in the distance walked in 6 min than patients undergoing the same program without additional NIPPV treatment (left).

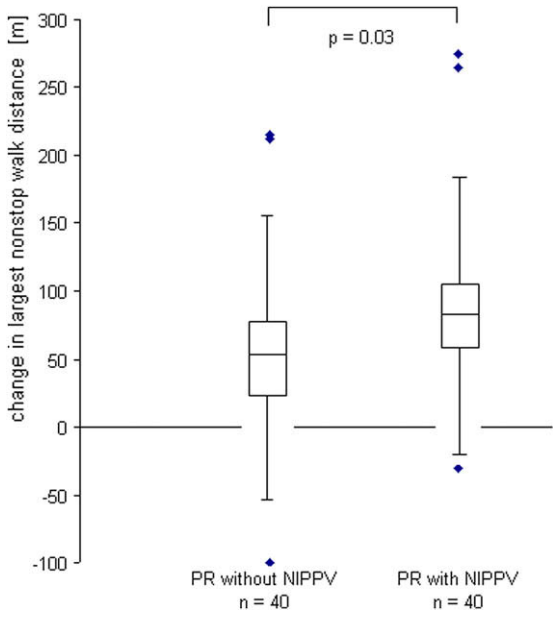

Figure 2 Changes in largest non-stop walk distance from baseline to the end of a 29-day, hospital-based, intensive pulmonary rehabilitation (PR) program. Patients who had been started on nocturnal NIPPV at the beginning of the rehabilitation program (right) revealed significantly better increases in the largest non-stop walk distance than patients undergoing the same program without additional NIPPV treatment (left).

demonstrate beneficial physiologic effects of NIPPV as an adjunct to an outpatient PR program.

The PR effects in patients without receiving NIPPV were comparable to previous, controlled studies. Salman et al.[5] analyzed six studies of COPD patients with similar baseline FEV_1 as in our cohort. These patients underwent 8 weeks to 12 months outpatient PR and developed increases in 6MWD with an ES of 0.63. However, outpatient PR programs with less than 3 months duration did not provide any relevant benefit in severe COPD. A previous meta-analysis, published by Lacasse et al. in 1996,[4] analyzed 11 studies with similar COPD patients. Most studies included were performed in an outpatient setting, and 6 weeks to 6 months PR resulted in an average increase of 6MWD of 55.7 m with an average effect size of 0.6. The PR program in the current study was shorter but more intense, included only patients in GOLD stage IV, and its effects seem to equal previous outpatient PR studies.

The combination of PR and nocturnal NIPPV produced additional improvements in 6MWD, the largest non-stop walking distance, another surrogate of endurance,[30] FEV_1, and lung hyperinflation. Since the largest non-stop walk distance was determined during the 6-minute walk test, a test assessing the submaximal level of exercise capacity, the 'real' largest non-stop walk distance might have been underestimated in some patients who continuously walked until the test was terminated after 6 min.

The current trial demonstrates comprehensively the benefits of NIPPV as an adjunct to COPD rehabilitation, regarding functional capacity and HRQL. This extends the observations of two previous trials investigating nocturnal NIPPV in outpatient rehabilitation of COPD patients. Garrod et al.[10] demonstrated in NIPPV treated subjects a statistical significant increase of 100 m in shuttle walk tests performed before and after 8 weeks PR training, compared to 28 m in the control group. Apart from an improvement in fatigue, no significant differences were documented for activities of daily living or anxiety between patients with or without NIPPV treatment. With a similar study design, Duiverman et al.[11] found no significant changes in functional capacity after three months outpatient rehabilitation, but their assessment of HRQR revealed positive effects on fatigue and cognition. These studies and our results suggest an important influence of nocturnal NIPPV on the effectiveness of PR. However, the ''pure'' effect of NIPPV could not been determined in either study. In the current study, we were not able to introduce a third limb with patients receiving NIPPV without undergoing PR. NIPPV without exercise training was previously evaluated in a meta-analysis by Wijkstra et al.,[31] which included two small studies. The average increase in 6MWD was calculated on 27.5 m for patients using NIPPV over three months.

Table 2 Outcome of pulmonary rehabilitation in COPD patients with/without NIPPV. For abbreviations refer to Table 1.

	PR with NIPPV, $n = 40$					Control group (PR without NIPPV), $n = 40$					p-Value for changes between groups
	Baseline	Post-PR	95% CI of changes within the NIPPV group	p	Effect size	Baseline	Post-PR	95% CI of changes within the control group	p	Effect size	
FEV_1 [l]	0.72	0.79	0.04—0.13	0.25		0.69	0.67	−0.04 to 0.01	0.55		<0.001
FEV_1% predicted	26.4	30.0	0.6—8.5	0.16		25.5	25.1	−1.8 to 0.7	0.73		0.001
TLC% predicted	131.4	128.9	−7.5 to 3.8	0.64		139.2	140.9	−4.6 to 6.7	0.65		0.28
RV/TLC [%]	75.2	72.2	−5.79 to −0.34	0.04		76.7	77.0	−1.4 to 1.9	0.79		0.04
pO_2 [mmHg]	53.4	58.2	0.1—3.9	0.04		56.2	57.4	−2.9 to 3.1	0.59		0.78
PCO_2 [mmHg]	53.8	46.7	−5.6 to −9.4	<0.01		51.7	50.1	−2.6 to 2.1	0.8		0.36
6MWD [m]	243	325	60.6—101.8	<0.01	0.89	245	295	35.6 to 63.1	0.02	0.58	0.04
Largest non-stop walk distance [m]	219	308	60.6—110.6	<0.01	0.74	210	261	39.5 to 82.3	0.04	0.47	0.03

Table 3 Subgroup analysis of patients with a baseline $PCO_2 \leq 50$ mmHg ($n = 28$). For abbreviations refer to Table 1.

	PR with NIPPV, $n = 14$					Control group (PR without NIPPV), $n = 14$					p-Value for changes between groups
	Baseline	Post-PR	95% CI of changes within the NIPPV group	p	Effect size	Baseline	Post-PR	95% CI of changes within the control group	p	Effect size	
FEV_1 [l]	0.82	0.91	0.05 to 0.16	0.52		0.82	0.74	−0.07 to 0.05	0.35		0.01
FEV_1% predicted	29.5	33.3	1.97 to 5.66	0.34		30.8	29.7	−2.6 to 2.3	0.62		0.01
TLC % predicted	131.1	126.1	−8.87 to 5.03	0.64		133.0	135.5	−4.7 to 7.1	0.66		0.42
RV/TLC [%]	73.7	69.8	−12.17 to −1.56	0.37		71.6	73.5	−1.9 to 3.0	0.38		0.02
pO_2 [mmHg]	56.3	60.8	−1.63 to 8.51	0.27		60.9	60.6	−3.6 to 3.0	0.9		0.17
PCO_2 [mmHg]	44.0	40.1	−9.34 to −1.25	0.37		44.2	41.1	−4.43 to 2.81	0.58		0.23
6MWD [m]	244	340	59 to 132	0.01	0.97	251	306	36 to 72	0.1	0.59	0.03
Largest non-stop walk distance [m]	231	334	58 to 147	0.02	0.87	202	265	26 to 99	0.17	0.48	0.03

This increase, attributable to NIPPV, is of the same magnitude as the differences in the current study found for 6MWD improvements in patients with or without NIPPV (82 *versus* 50 m).

Analysing physiologic causality of our observations was beyond the scope of this study. However, positive pressure ventilation provides direct mechanical support for the overloaded ventilatory muscles in severe COPD.[32] More importantly, positive pressure ventilation may allow recuperation of breathing muscles and restoration of their energy stores.[33,34] In addition, improved bronchial airflow limitation and pulmonary hyperinflation reduce of the work of breathing.[35] These mechanisms may contribute to the better exercise tolerance in NIPPV treated subjects. The impact of mechanical ventilation on the central control of breathing[36] may be an additional factor.

Previous investigators provided long-term NIPPV treatment only for patients with some degree of hypercapnia, an indicator for exhausted ventilatory muscles.[37,38] However, nothing is known about the effects of nocturnal NIPPV on exercise capacity in COPD patients with normal or only slightly elevated daytime PCO_2. The present study enrolled patients and applied NIPPV, regardless of their baseline PCO_2 levels. Interestingly, subgroup analyses in patients with a baseline PCO_2 below 50 mmHg revealed similar effects in the main outcome parameters (Table 3), compared to the whole cohort. These observations favour the concept of early implementation of positive pressure ventilatory support in PR patients with severe COPD. Further clinical and physiologic data are needed to support these preliminary observations.

Apart from polysomnographies in 16 patients with difficulties during the implementation of nocturnal NIPPV, we were not able to perform sleep studies in all patients to determine the impact of nocturnal NIPPV on the sleep quality. The results of the SF-36 questionnaire suggest

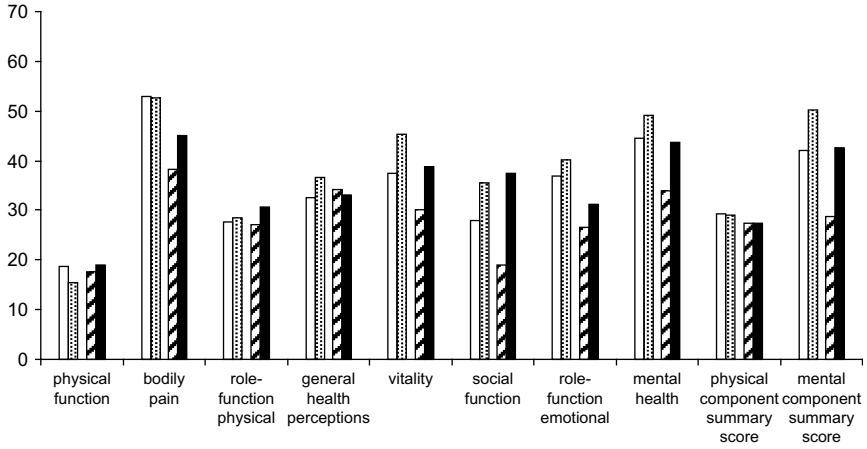

Figure 3 Health-related quality of life before and after pulmonary rehabilitation with/without NIPPV. SF-36 scores reflecting health-related quality of life. Assessments were made in the control group at baseline (white columns) and after the 29 days rehabilitation program (dotted columns). The same assessments were made in the NIPPV group at baseline (hatched columns) and after the 29-day pulmonary rehabilitation program (black columns). In the control group, clinically relevant improvements were detected for vitality only, while patients in the NIPPV group developed relevant improvements in role-function physical, vitality, social function, mental health, and the mental component summary score. For details refer to main text and Table 4.

Table 4 Health-related quality of life before and after pulmonary rehabilitation with/without NIPPV. Subscores and summary scores of the SF-36 questionnaire at baseline and after pulmonary rehabilitation (PR) with or without NIPPV. An effect size of 0.20 is small, 0.50 is moderate, and >0.80 is large.[24]

	PR with NIPPV, $n = 35$			PR without NIPPV, $n = 34$		
	Baseline	Post-PR	Effect size	Baseline	Post-PR	Effect size
Physical function	17.6 ± 16.5	19.0 ± 14.5	0.08	18.8 ± 15.0	15.6 ± 13.6	−0.22
Bodily pain	38.3 ± 14.5	45.1 ± 12.6	0.47	53.0 ± 11.2	52.5 ± 10.8	−0.05
Role-function physical	27.0 ± 6.0	30.7 ± 14.5	**0.61**	27.8 ± 8.4	28.6 ± 10.4	0.07
General health perceptions	34.2 ± 4.3	33.1 ± 9.6	−0.26	32.6 ± 12.9	36.5 ± 10.6	0.31
Vitality	30.0 ± 10.6	38.8 ± 13.1	**0.83**	37.5 ± 11.6	45.3 ± 9.6	**0.67**
Social function	19.1 ± 15.8	37.4 ± 21.9	**1.16**	28.0 ± 20.5	35.5 ± 19.2	0.36
Role-function emotional	26.5 ± 15.5	31.1 ± 20.1	0.30	37.0 ± 20.1	40.3 ± 19.8	0.16
Mental health	33.9 ± 17.0	43.6 ± 18.2	**0.57**	44.4 ± 13.0	49.1 ± 12.1	0.36
Physical component summary score	27.3 ± 10.1	27.3 ± 12.5	0.00	29.4 ± 11.6	29.0 ± 8.4	−0.03
Mental component summary score	28.8 ± 19.1	42.7 ± 23.6	**0.73**	42.1 ± 18.0	50.1 ± 15.1	0.44

satisfactory recuperation during sleep in NIPPV patients. The categories vitality and social function improved with large effect sizes, and mental health, role-function physical, and mental sum score improved with moderate ES. In contrast, patients without NIPPV revealed moderate improvements in vitality, but no relevant changes in any of the other categories.

The length of PR (and study participation) varied between three and five weeks with an average of 29.4 days. The only reasons for these variations were differences in cost reimbursement of the patients' health care insurance, a random variable not influenced by the investigators.

The lack of a prospective, randomized design for assessment of functional capacity and HRQL, and the non-blinding of subjects and investigators to the intervention NIPPV are acknowledged limitations of the current study. The protocol did not provide repeated measurements of functional status or assessment of HRQL during PR, therefore we were not able to evaluate rehabilitation progress over the time. Similar to many previous PR studies, we were not able to perform follow-up observations of the participants after discharge from PR. Therefore, we had no opportunity to estimate the impact of the rehabilitation results on ability to work, limitations of physical exertion, or social activities. The strengths of the presented study are the large, homogeneous, and well-matched cohorts of patients, who underwent a standardized, hospital-based PR program. The rationale for the current study was a proof of concept, and these data may serve as the basis for prospective, randomized controlled trials with large study populations and observations beyond the period of PR.

In conclusion, NIPPV is a feasible and beneficial tool in hospital-based PR. Patients with severe COPD benefit from a structured PR program, and improvements in functional capacity and health-related quality of life can be amplified, if PR is combined with nocturnal noninvasive positive pressure ventilation. Comparable treatment effects had been found for patients with either normocapnia or only mild hypercapnia, and severe hypercapnia at study entry.

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Conflict of interest

T.K. received fees for lectures and travel grants for scientific meetings from Resmed. All other authors have no conflict of interest.

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